VIII. QUANTIFICATION OF TOXICOLOGIC EFFECTS

Introduction

The quantification of toxicologic effects of a chemical consists of separate assessments of noncarcinogenic and carcinogenic health effects. Chemicals that do not produce carcinogenic effects are believed to have a threshold dose below which no adverse, noncarcinogenic health effects occur, while carcinogens are assumed to act without a threshold.

In the quantification of noncarcinogenic effects, a Reference Dose (RfD), [formerly termed the Acceptable Daily Intake (ADI)] is calculated. The RfD is an estimate (with uncertainty spanning perhaps an order magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious health effects during a lifetime. The RfD is derived from a no-observed-adverse-effect level (NOAEL), or lowest-observed-adverse-effect level (LOAEL), identified from a subchronic or chronic study, and divided by an uncertainty factor(s) times a modifying factor. The RfD is calculated as follows:

$$RfD = \frac{(NOAEL \text{ or } LOAEL)}{[Uncertainty \text{ } Factor \text{ } (s) \text{ } x \text{ } Modifying \text{ } Factor]} = \_\_ \text{ } mg/kg/day$$

Selection of the uncertainty factor to be employed in the calculation of the RfD is based upon professional judgment, while considering the entire data base of toxicologic effects for the chemical. In order to ensure that uncertainty factors are selected and

applied in a consistent manner, the U.S. EPA (1994) employs a modification to the guidelines proposed by the National Academy of Sciences (NAS, 1977, 1980) as follows:

Standard Uncertainty Factors (UFs)

- Use a 10-fold factor when extrapolating from valid experimental results from studies using prolonged exposure to average healthy humans. This factor is intended to account for the variation in sensitivity among the members of the human population. [10H]

- Use an additional 10-fold factor when extrapolating from valid results of long-term studies on experimental animals when results of studies of human exposure are not available or are inadequate. This factor is intended to account for the uncertainty in extrapolating animal data to the case of humans. [10A]

- Use an additional 10-fold factor when extrapolating from less than chronic results on experimental animals when there is no useful long-term human data. This factor is intended to account for the uncertainty in extrapolating from less than chronic NOAELs to chronic NOAELs. [10S]

- Use an additional 10-fold factor when deriving an RfD from a LOAEL instead of a NOAEL. This factor is intended to account for the uncertainty in extrapolating from LOAELs to NOAELs. [10L]

Modifying Factor (MF)

- Use professional judgment to determine another uncertainty factor (MF) that is greater than zero and less than or equal to 10. The magnitude of the MF depends upon the professional assessment of scientific uncertainties of the study and data base not explicitly treated above, e.g., the completeness of the overall data base and the number of species tested. The default value for the MF is 1.

The uncertainty factor used for a specific risk assessment is based principally upon scientific judgment rather than scientific fact and accounts for possible intra- and

interspecies differences. Additional considerations not incorporated in the NAS/ODW guidelines for selection of an uncertainty factor include the use of a less than lifetime study for deriving an RfD, the significance of the adverse health effects and the counterbalancing of beneficial effects.

From the RfD, a Drinking Water Equivalent Level (DWEL) can be calculated. The DWEL represents a medium specific (i.e., drinking water) lifetime exposure at which adverse, noncarcinogenic health effects are not anticipated to occur. The DWEL assumes 100% exposure from drinking water. The DWEL provides the noncarcinogenic health effects basis for establishing a drinking water standard. For ingestion data, the DWEL is derived as follows:

$$DWEL = \frac{(RfD)\ x\ (Body\ weight\ in\ kg)}{Drinking\ Water\ Volume\ in\ L/day} = \_\_\ mg/L$$

where:

Body weight = assumed to be 70 kg for an adult
Drinking water volume = assumed to be 2 L/day for an adult

In addition to the RfD and the DWEL, Health Advisories (HAs) for exposures of shorter duration (1-day, 10-day and longer-term) are determined. The HA values are used as informal guidance to municipalities and other organizations when emergency spills or contamination situations occur. The HAs are calculated using an equation similar to the RfD and DWEL; however, the NOAELs or LOAELs are identified from acute or subchronic studies. The HAs are derived as follows:

$$HA = \frac{(NOAEL \text{ or } LOAEL) \times (bw)}{(UF) \times (\_\_\_\_\ L/day)} = \_\_\_\ mg/L$$

Using the above equation, the following drinking water HAs are developed for noncarcinogenic effects:

1. 1-day HA for a 10 kg child ingesting 1 L water per day.
2. 10-day HA for a 10 kg child ingesting 1 L water per day.
3. Longer-term HA for a 10 kg child ingesting 1 L water per day.
4. Longer-term HA for a 70 kg adult ingesting 2 L water per day.

The 1-day HA calculated for a 10 kg child assumes a single acute exposure to the chemical and is generally derived from a study of <7 days duration. The 10-day HA assumes a limited exposure period of 1-2 weeks and is generally derived from a study of <30 days duration. The longer-term HA is derived for both the 10 kg child and a 70 kg adult and assumes an exposure period of ~7 years (or 10% of an individual's lifetime). The longer-term HA is generally derived from a study of subchronic duration (exposure for 10% of animal's lifetime).

The U.S. EPA categorizes the carcinogenic potential of a chemical, based on the overall weight-of-evidence, according to the following scheme:

Group A: Human Carcinogen. Sufficient evidence exists from epidemiology studies to support a causal association between exposure to the chemical and human cancer.

Group B: Probable Human Carcinogen. Sufficient evidence of carcinogenicity in animals with limited (Group B1) or inadequate (Group B2) evidence in humans.

Group C: Possible Human Carcinogen. Limited evidence of carcinogenicity in animals in the absence of human data.

Group D: Not Classified as to Human Carcinogenicity. Inadequate human and animal evidence of carcinogenicity or for which no data are available.

Group E: Evidence of Noncarcinogenicity for Humans. No evidence of carcinogenicity in at least two adequate animal tests in different species or in both adequate epidemiologic and animal studies.

If toxicologic evidence leads to the classification of the contaminant as a known, probable or possible human carcinogen, mathematical models are used to calculate the estimated excess cancer risk associated with the ingestion of the contaminant in drinking water. The data used in these estimates usually come from lifetime exposure studies using animals. In order to predict the risk for humans from animal data, animal doses must be converted to equivalent human doses. This conversion includes correction for noncontinuous exposure, less than lifetime studies and for differences in size. The factor that compensates for the size difference is the cube root of the ratio of the animal and human body weights. It is assumed that the average adult human body weight is 70 kg and that the average water consumption of an adult human is 2 L of water per day.

For contaminants with a carcinogenic potential, chemical levels are correlated with a carcinogenic risk estimate by employing a cancer potency (unit risk) value together with the assumption for lifetime exposure from ingestion of water. The cancer unit risk is usually derived from a linearized multistage model with a 95% upper confidence limit providing a low dose estimate; that is, the true risk to humans, while not identifiable, is not likely to exceed the upper limit estimate and, in fact, may be lower. Excess cancer risk estimates may also be calculated using other models such as the one-hit, Weibull, logit and probit. There is little basis in the current understanding of the biologic mechanisms

involved in cancer to suggest that any one of these models is able to predict risk more accurately than any other. Because each model is based upon differing assumptions, the estimates derived for each model can differ by several orders of magnitude.

The scientific data base used to calculate and support the setting of cancer risk rate levels has an inherent uncertainty that is due to the systematic and random errors in scientific measurement. In most cases, only studies using experimental animals have been performed. Thus, there is uncertainty when the data are extrapolated to humans. When developing cancer risk rate levels, several other areas of uncertainty exist, such as the incomplete knowledge concerning the health effects of contaminants in drinking water, the impact of the experimental animal's age, sex and species, the nature of the target organ system(s) examined and the actual rate of exposure of the internal targets in experimental animals or humans. Dose-response data usually are available only for high levels of exposure and not for the lower levels of exposure closer to where a standard may be set. When there is exposure to more than one contaminant, additional uncertainty results from a lack of information about possible synergistic or antagonistic effects.

Current Levels of Exposure

Monochloramine has been used as a disinfectant of drinking water. An inventory of municipal water supplies done in the early 1960s revealed that 308 of 11,590 supplies surveyed used an ammonia chlorine process (Moore and Calabrese, 1980).

According to Morris et al. (1980), the extent of knowledge of natural water contamination by N-containing aromatic compounds or the degree to which these compounds react with aqueous chlorine is very limited. It is known that both inorganic chloramines and organic N-chloramines are found upon chlorination of wastewater effluents (Isaac and Morris, 1980). One survey reported the presence of monochloramine ranging from 0.0321-0.9979 mg/L and dichloramine ranging from 0.0020-0.6950 mg/L in secondary sewage effluents and cooling water samples (Jolley et al., 1978). Because inorganic and organic chloramines cannot be identified separately, the levels are based on the mixture.

Noncarcinogenic Effects

The chlorination of water containing ammonia or organic amines may result in the formation of monochloramine, dichloramine, and trichloramine (nitrogen trichloride) through the reaction between ammonia and hypochlorous acid. The amount of chloramines produced depends upon the levels of chlorine and ammonia, and the pH of the water being treated. Some studies on the oral effects of chloramines were presented in Tables V-1 and V-2.

Results on the mutagenicity of chloramines are inconclusive. Chloramine is weakly mutagenic for *Bacillis subtilis* and causes DNA breaks in this bacterial species (Lu Shih and Lederberg, 1976). Thomas et al. (1987) reported that monochloramine (40 um) marginally increased the numbers of revertant colonies over untreated control levels in assays employing *Salmonella typhimurium* (TA97, TA100 and TA102). Monochloramines

produce chromosome abnormalities in both *Vicia faba* and rodent cells (Fetner, 1962; NIEHS, 1982). It was responsible for cellular hypertrophy, increased mitotic figures and bizarre chromatin patterns in B6C3F1 mice exposed to 200 and 400 mg/L in drinking water (Wolfe et al., 1984), while Meier et al. (1985) found that monochloramine at 0, 40, 100 and 200 mg/L did not induce chromosomal aberrations or micronuclei in bone marrow of CD-1 mice or spermhead abnormalities in B6C3F1 mice. Organic chloramines are mutagenic or bacteriotoxic in *S. typhimurium* and have been reported to produce SCEs and other chromosomal changes in mammalian cells (Scully et al., 1983; Bempong and Scully, 1980b; Bempong et al., 1981, 1986; Scully and Bempong, 1982). Tests for teratogenic, reproductive and carcinogenic effects have been negative or inconclusive.

Abdel-Rahman et al. (1984) investigated the toxicity of monochloramine (NH_2Cl) in groups of four male Sprague-Dawley rats/treatment weighing ~160 g. Acute exposure to a single dose at 10 (0.19 mg/kg/day), 20 (0.38 mg/kg/day) or 40 (0.75 mg/kg/day) mg/L NH_2Cl induced a significant increase in blood glutathione levels within 30 minutes after administration of 3 mL aqueous solution by gavage. As part of the same study, the long-term toxicity of NH_2Cl in drinking water was also investigated. Groups of four male Sprague-Dawley rats drank either 0, 1 (0.067 mg/kg/day), 10 (0.67 mg/kg/day) or 100 (6.7 mg/kg/day) mg/L NH_2Cl in deionized water daily for $\leq$12 months. The levels of chlorine, dichloramine and trichloramine in the NH_2Cl solution were <1%, <1% and 0% respectively of the total NH_2Cl added. Food was available *ad libitum* and body weight was measured during the treatment. Heparinized blood was collected by cardiac puncture at 2, 4, 6, 8, 10 and 12 months after treatment, and blood GSH and osmotic fragility were determined

at each of these intervals. Results varied over the 12-month study period, but at 6 and 12 months after initiation of the study, statistically lower GSH levels were observed in all treated rats. After 3 months of treatment significant decreases in RBC count and hematocrit were observed at the higher dosage levels. Hemoglobin concentration and MCH decreased significantly in the 100 mg/L group after 10 months of treatment. The health significance of these types of changes is uncertain. Furthermore, results of treatment effects were analyzed by inappropriate statistical methods (ANOVA). The multiple comparison test used for paired comparisons (Duncan's) is a nonconservative appproach. A more conservative approach would have taken into account correlations or nonindependences. In addition, the control variability was greater than variability between dose groups. A number of "significant" changes in hematologic parameters relative to control values were identified that had no consistent relationship with dose and were not observed consistently throughout the period of exposure. This could be due to the use of a multiple comparison procedure, which is liberal such as the Duncan's.

Several short-term studies showed no observed adverse hematologic effects in mice, rats and monkeys (Moore et al., 1980; Bercz et al., 1982; Bull, 1980). In A/J mice administered chloramine solutions between 2.5 and 200 mg/L (pH 8.9) for 30 days, the only observable effect was a slight increase in hematocrit (Moore et al., 1980). In another study of similar duration (45 days) rats treated with 10, 50 or 100 mg/L monochloramine experienced a decrease in the amount of methemoglobin present in the blood, the opposite of what was expected (Bull, 1980). Bercz et al. (1982) studied the toxicity of monochloramine administered in drinking water to 5 adult male and 7 adult female African

Green monkeys (3.0-5.7 kg). Monochloramine was administered for 6 weeks at 0 and 100 mg/L. The authors estimated the mean daily dose at ~10 mg/kg/day. Treatment with monochloramine had no detectable effect in 18 hematologic tests on the 12 monkeys, including red cell GSH levels. No evidence of thyroid suppression was detected from measurements of serum T_4. The results of these data are somewhat conflicting in that similar dose levels and duration produced different changes, if any, in hematologic parameters. One explanation for the varying observations between laboratories may be the conditions under which the solutions of monochloroamine were generated.

In 1981 a draft report investigated the effects of monochloramine in Fischer 344 rats and B6C3F1 mice (GSRI, 1981). Rats and mice (10 animals/sex/group) were administered concentrations of 0, 25, 50, 100, 200 and 400 ppm monochloramine in drinking water for 91 days. Using food and water consumption data provided in the report, corresponding dose levels are as follows: 2.5, 4.9, 10.2, 18.8, 40.7 mg/kg/day for male rats; 3.8, 6.5, 13.8, 26.6, 53.9 mg/kg/day for female rats; 4.9, 8.3, 14.5, 31.3, 50.7 mg/kg/day for male mice; 7.7, 12.1, 21.9, 34.6, 88.5 mg/kg/day for female mice. After 25 days the buffer system for monochloramine was changed because of a palatibility problem at the higher dose levels. Decreased body weight gain and decreased relative liver weight were observed in male and female rats at concentrations of 200 and 400 mg/L. A statistical analysis was not provided. Protein excretion increased in male rats only when 200 and 400 mg/L monochloramine was administered. Microscopic examination of rat tissues at the 400 ppm level did not reveal any treatment-related lesions.

As with rats, male and female mice gained less weight than the controls at the 200 and 400 ppm levels. There was a reduction in absolute liver weights and liver-to-body weight ratios in male mice at the 400 ppm level and in female mice at $\geq$100 ppm. Histopathologic observations revealed mild to moderate cytologic alteration in male mice administered 200 and 400 ppm levels. Chronic liver inflammatory changes occurred at 100, 200 and 400 ppm in female mice and to a lesser extent in male mice at the 100 ppm level. At concentrations of 100, 200 and 400 ppm increased frequency of mitotic figures, hypertrophy and unusual chromatin patterns occurred in males and in a female at $\geq$200 ppm. The results suggest a LOAEL for liver toxicity of 100 ppm and a NOEL of 50 ppm based on chronic liver inflammatory changes in mice.

Daniel et al. (1990) administered 0, 25, 50, 100 and 200 mg/L monochloramine to male and female Sprague-Dawley rats (10/sex/dose) in their drinking water for 90 consecutive days. These doses correspond to 0, 1.8, 3.4, 5.8 and 9.0 mg/kg/day for males and 0, 2.6, 4.3, 7.7 and 12.1 mg/kg/day for females. At $\geq$50 mg/L in males there were reductions in body weight gain with significant reductions only at the highest dose (200 mg/L). For males and females in the 200 mg/L dose group the average weight gain was 51% of that of the controls; however, water consumption for the 200 mg/L dose was 31 and 33% of controls for males and females, respectively. At the 200 mg/L dose level there were also reductions in organ weights (absolute, relative or both) and liver and spleen weight reductions in both sexes. Although authors concluded that 100 mg/L dose is considered the NOAEL, they suggest that a matched watering and feeding study would be

useful for distinguishing between systemic toxic effects and weight loss from taste aversion to more clearly identify the NOAEL.

Daniel et al. (1991) administered 0, 12.5, 25, 50, 100 and 200 mg/L monochloramine to male and female B6C3F1 mice (10/sex/dose). These doses correspond to 0, 2.5, 5.0, 8.6, 11.1 and 15.6 mg/kg/day for males and 0, 2.8, 5.3, 9.2, 12.9 and 15.8 mg/kg/day for females. Water consumption was decreased in all treated groups. There were significant water and food consumption decreases and weight gain reductions at the two highest dose groups. There were reductions in absolute and relative organ weights in male and female mice in the two highest dose groups. Based on relatively minor changes at 100 mg/L) including <10% decrease in body weight gain at 100 mg/L, and 19-25% decrease in body weight gain at 200 mg/L, a NOAEL of 100 mg/L (12.9 mg/kg/day) was identified based on a decrease in body weight gain and decreased organ weights in B6C3F1 mice consuming 200 mg/L monochloramine in the drinking water for 90 days. The authors state that the lower levels of serum enzyme and reduced organ weights were considered consistent with decreased water and nutrient consumption and altered electrolyte balance rather than disinfectant-induced toxicity. The authors conclude that the absence of histopathology or observable clinical signs of toxicity suggest that these monochloramine exposures induce a relatively mild, nonspecific toxicity by an indirect mechanism (nutritional and electrolyte deficiencies) rather than a direct toxicologic effect on specific organs or tissues.

NTP (1990) conducted 2-year studies using monochloramine administered in the drinking water. In the first study monochloramine was administered to male and female

F344/N rats at 0, 50, 100 and 200 ppm. These doses were calculated on a time-weighted average to be 0, 2.1, 4.8 and 8.7 mg/kg/day for males and 0, 2.8, 5.3 and 9.5 mg/kg/day for females. Mean body weights of high-dose rats were lower than their respective controls. However, mean body weights of rats receiving chloraminated drinking water were within 10% of controls until week 97 for females and week 101 for males. Interim evaluations made at 14 weeks revealed that body weights of high-dose males were lower than controls. At the 66-week evaluation, there was a dose-related decrease in body weight in male chloraminated-treated rats and the mean body weights of high-dose rats were 94% and 92% of controls for males and females, respectively. Decreases in liver and kidney weight in the high-dose males and increases in brain and kidney-to-body weight ratios in high-dose male and female rats were observed in the 14- and 66-week evaluations.

The NTP (1990) second study was a 2-year study of momochloramine administered in drinking water to male and female B6C3F1 mice at 0, 50, 100 and 200 ppm. These doses were calculated on a time-weighted average to be 0, 5.0, 8.9 and 15.9 mg/kg/day for males and 0, 4.9, 9.0 and 17.2 mg/kg/day for females. Mean body weights of high-dose male mice were 10-22% lower than controls after week 37 and the body weights of high-dose female mice were 10-35% lower after week 8. At the 15-week interim sacrifice the mean body weights of high-dose mice were 91% and 84% of controls for males and females, respectively. At the 66-week evaluation the differences in body weight between the high-dose and controls was 87% for females but 91% of controls for the mid- and high-dose males. Decreases in liver weights and increases in brain and

kidney-to-body weight ratios were observed in high-dose male and female mice at 15 and 66 weeks.

Quantification of Noncarcinogenic Effects

Derivation of 1-Day Health Advisory. The only report of an acute exposure to monochloramine in the literature is the study by Abdel-Rahman et al. (1984) wherein the authors observed a drop in blood GSH levels at the lowest dose administered by gavage (3 mL of 10 mg/L solution). As the health implications of these effects are uncertain, they were transitory and were not corroborated by other investigations, it would seem inappropriate to use this study as the basis for a 1-day HA. Therefore, no suitable study is available for the derivation of a 1-day HA. It is recommended that the 10-day HA of 1.0 mg/L be adopted as the 1-day HA.

Derivation of 10-Day Health Advisory. Similar NOAELs or NOELs for monochloramine of 200, 100 and 100 ug/L for hematologic parameters were identified by Bercz et al. (1982), Moore et al. (1980) and Bull (1980), respectively. Both Moore et al. (1980) and Bull (1980) did observe some changes in hematologic parameters. Moore et al. (1980) found a slight increase in hematocrit in A/J mice after 30 days of exposure whereas after 45 days of exposure to rats there was a decrease in the amount of methemoglobin present in the blood, the opposite of what was expected (Bull, 1980). Bercz et al. (1982) reported a NOEL in monkeys after treatment with 100 mg/L chloramines in drinking water. There were no detectable effects in 18 hematologic tests. The authors calculated that by the termination of the study the test animals were

consuming 10 mg chloramine/kg/day. One explanation for the varying observations between laboratories may be the conditions under which the solutions of monochloramine were generated. It is recommended that the NOEL of 100 mg/L from the Bercz et al. (1982) study be used to derive the 10-day HA for two reasons: 1) the Bull (1980) study provides an incomplete description of methods concerning study design and clinical analysis, and 2) monkeys may be a better animal model since the A/J strain of mice used in the Moore et al. (1980) study maintain an erythrocyte glucose-6-phosphate dehydrogenase activity 3 times that of human cells and may be more resistant to oxidant stress (Kiese, 1974). A NOEL is, therefore, set at 10 mg/kg/day, which the authors determined to be the rate of consumption of chloramine at the 6-week termination of the study.

A provisional 10-day HA is calculated as follows:

For a 10 kg child:

$$10\text{-}day\ HA = \frac{10\ mg/kg/day\ x\ 10\ kg}{100\ x\ 1\ L/day} = 1\ mg/L$$

where:

10 mg/kg/day	=	NOAEL based on the absence of hematologic effects in monkeys (Bercz et al., 1982)
10 kg	=	assumed body weight of a child
10	=	uncertainty factor for use of an animal NOAEL and to protect sensitive members of the human population
1 L/day	=	assumed water consumption of a child

Thus, the proposed 10-day HA is 1 mg/L for a 10 kg child. The small number of animals used by Bercz et al. (1982) and the lack of other shorter- term studies for supporting data should be considered when evaluating this HA.

Derivation of Longer-Term HA. Several longer-term studies were considered for serving as the basis for the longer-term HA. The 1981 draft report by GSRI had methodology and data inconsistencies that make it unsuitable for a longer-term HA. In the Daniel et al. (1990) study, male and female rats in the 200 mg/L dose group (highest dose tested) had an average weight gain of 51% of controls and drinking water consumption was decreased 31-34%, which may suggest that the effect of weight loss may be due to a taste aversion rather than a systemic toxic effect. Although the authors identified a NOAEL of 100 mg/L (5.8 and 7.7 mg/kg/day) they also suggested that the NOAEL could be more clearly identified by a matched feeding and water study to more clearly distinguish between systemic toxic effects and weight loss from taste aversion. In the Daniel et al. (1991) study a NOAEL of 50 mg/L (8.6-9.2 mg/kg/day) was identified for B6C3F1 mice. At the two higher dose levels tested, the lower levels of serum enzymes and reduced organ weights were considered by the authors to be consistent with decreased water and nutrient consumption and altered electrolyte balance rather than chemical-induced toxicity. The studies by Daniel et al. are supportive of the NTP (1990) study, which is used as the basis for the DWEL. Using the data from either of the two studies by Daniel et al. would result in a longer-term HA of 3 mg/L, slightly less than the DWEL of 4 mg/L. The DWEL is based on a well conducted chronic NTP (1990) study with a NOAEL of 9.5 mg/kg/day. Because of the problems in interpreting the subchronic studies, it is recommended that the

DWEL of 4 mg/L be adopted for the longer-term HA for adults. For the 10 kg child drinking 1 L/day, the DWEL is modified resulting in a longer-term HA of 1 mg/L.

Assessment of Lifetime Exposure and Derivation of a DWEL. It is recommended that the study by NTP (1990) be used as a basis for a DWEL because it is a chronic 2-year study using rats and mice with chloramine in the drinking water. When monochloramine was administered to rats and mice in their drinking water there were statistically significant changes in body and several organ weights (as previously described) at the high-dose level. However, the significance of these changes is unclear because test animals consumed a reduced amount of water, which was perhaps due to palatability, and NTP does not consider these changes in body and organ weight biologically significant. It is recommended that the highest dose tested be used as the NOAEL. The NOAEL identified in the rat study was chosen over the NOAEL in the mouse study to calculate the proposed RfD because data from acute and shorter term studies indicate that the rat is the more sensitive species. The calculation of the RfD is as follows:

$$RfD = \frac{9.5\ mg/kg/day}{100} = 0.095\ mg/kg/day \quad (rounded\ to\ 0.1\ mg/kg/day)$$

where:

9.5 mg/kg/day = NOAEL based on an absence of biologically significant adverse effects in rats (NTP, 1990)

100 = uncertainty factor for protection of sensitive members of the human population and for use of an animal NOAEL

$$DWEL = \frac{0.1\ mg/kg/day\ x\ 70\ kg}{2\ L/day} = 3.5\ mg/L\ (rounded\ to\ 4\ mg/L)$$

where:

0.1 mg/kg/day	=	RfD
2 L/day	=	assumed water consumption by an adult
70 kg	=	assumed body weight of an adult

The RfD of 0.1 mg/kg/day was verified (06/23/92) by the RfD/RfC Work Group of the U.S. EPA (1994). The Work Group expressed a high degree of confidence in the critical study. Although ideally higher doses should have been tested, this was not possible due to the taste aversion. The study by NTP (1990) examined relevant endpoints in two animal species exposed to chloramine by a relevant route of exposure for a prolonged period of time. Several dosage levels were included, the number of animals per dose group was adequate, and the statistical analyses were used. The Work Group expressed a medium level of confidence in the data base. Information is available on mice, rat and monkeys for the noncarcinogenic toxicity of oral exposure to monochloramine for subchronic periods. The developmental toxicity and reproductive toxicity of monochloramine have been examined in rats but a developmental toxicity study in a second species and a 2-generation reproductive study are not available. (Information available for chlorine can be used to satisfy data gaps for monochloramine.) Confidence in the data base is limited

by the lack of information on health effects in humans. Overall confidence in the RfD is considered to be medium. A summary of the HAs and DWEL is presented in Table VIII-1.

Carcinogenic Effects

In a 2-year study by NTP (1990), there was equivocal evidence of carcinogenic activity of chloraminated drinking water in female rats, which was due to the slightly increased incidence of mononuclear cell leukemia compared with that of controls. There was no

evidence of carcinogenic activity because of chloraminated drinking water in male rats or in male or female mice. Monochloramine was verified by the CRAVE Work Group (12/02/92) and is classified in group D, not classifiable as to human carcinogenicity, meaning that there is inadequate human and animal evidence of carcinogenicity (U.S. EPA, 1986).

Existing Guidelines, Recommendations and Standards

The NAS (1987) calculated a suggested no-adverse-response level (SNARL) of 0.581 mg/L. This was based on a NOEL of 50 ppm (estimated by NAS to be 8.3 mg/kg bw/day) from a 90-day study in mice, which showed reduced body weight and liver toxicity (GSRI, 1981). It was assumed that a 70 kg human consumes 2 L of water daily, which contributes 20% of total intake. This value should be viewed cautiously since the data in this study were not verified.

Special Groups at Risk

Long-term hemodialysis patients have displayed higher risks of hemolytic anemia caused by chloramines present in dialysis baths. These chloramines denature hemoglobin through oxidation and inhibit the hexose monophosphate shunt (Eaton et al., 1973). This problem can be eliminated by using charcoal-filtered water in the dialysis bath; therefore, this group should not be given special consideration in the development of water quality criteria (U.S. EPA, 1981).

Risk Characterization

In characterizing the risk that chloramines pose in drinking water, the health effects must be considered in light of the widespread use of the chloramine-ammonia process (chloramination) for disinfection purposes. As stated earlier in this document, the range of residual in the distribution system (1.5-2.5 mg/L) is well below the DWEL of 4 mg/L. In humans, health effects do not appear to be associated with levels of residual chloramine typically found in drinking water.